REMARKS

The Official Action dated September 8, 2005 has been carefully considered. Accordingly, the Amendment, taken with the following remarks, is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By present amendment, new claim 66 has been added and is directed to subject matter found on page 6, last paragraph, bridging to page 7, first paragraph. New claim 67 has also been added and is directed to subject matter found on page 17, lines 16-19 and the examples immediately following that disclosure and continuing to the top of page 22. As no new matter is involved in the addition of these dependent claims, Applicants respectfully request entry.

Claims 1, 4-14, 19 and 64-66 remain pending and are under examination.

35 U.S.C. § 112, first paragraph, "written description"

Claims 1, 4-14, 19 and 64 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that claims 1, 4-14, 19 and 64 encompass subject matter that is not defined in the specification. According to the Examiner, the claims are drawn to a method for inhibiting lipid oxidation associated with a condition in a patient, comprising administering to a patient a composition comprising a pharmacologically effective amount of an apolipoprotein (apo) A-IV peptide, to inhibit lipid oxidation, and that "the claimed invention asserts that the apo

A-IV is a peptide sequence of from 6-71 amino acids in length and wherein the peptide has substantially the same lipid oxidation properties as the apo A-IV molecule. The Examiner notes the present teachings at page 6 discussing the peptides made from apo A-I, their properties, and their efficacy in treating atherosclerosis, but asserts that the specification does not describe the specific structure and function of these sequence fragments. The Examiner further asserts that the limitation of 6-71 amino acids in length fails to define whether the sequence is derived from native apo A-IV, and that a sequence identifier has not been given to this sequence. The Examiner points to the present teachings that the lipid oxidation inhibiting peptides substantially correspond in sequence to amino acid sequences found in specific portions of apo A-IV, and asserts that this is an insufficient description since there are no characteristics or evidence provided to demonstrate retention of function with regard to inhibitory activity in lipid oxidation.

With respect particularly to claim 4, the Examiner asserts that the specification only "provides a generic description of how a variety of variants or fragments can be generated, and that no specific guidance is provided on generation of variants or fragments that demonstrate biological activity of the peptide sequence of SEQ ID NO 5." Broadly, the Examiner maintains that the Applicants are "not in possession of the apo A-IV, which comprises variants and fragments, which have substantially the same lipid oxidation properties as the apo A-IV wild-type molecule," and that there is no written description of either a representative number of the variants or of a common structural feature of the native apo A-IV that encompasses all the variants.

Summarily, the Examiner asserts that one of ordinary skill in the art "would not recognize from the disclosure that Applicants were in possession of the apo A-IV, which

comprises variants and fragments, which have substantially the same lipid oxidation properties as the apo A-IV wild type molecule," and that "there is no written description of either a representative number of the variants or of a common structural feature of the native apo A-IV that encompasses all the variants." This rejection is traversed and reconsideration is respectfully requested

With respect to arguments made in the Applicants' prior traversal, the Examiner concludes that they are unpersuasive. However, Applicants respectfully note that the prior rejection under this section was made under different bases, and therefore Applicants arguments were not intended to be persuasive as to these new issues.

Independent claim 1 recites a method for inhibiting lipid oxidation associated with a condition in a patient. The method comprises administering to a patient a composition comprising a pharmacologically effective amount of an apolipoprotein (apo) A-IV peptide to inhibit lipid oxidation. The apolipoprotein A-IV peptide is from 6 to 71 amino acids in length and the peptide has substantially the same lipid oxidation properties as the apolipoprotein A-IV molecule.

Independent claim 13 recites a method of inhibiting the progression of atherosclerosis in a patient in need thereof. The method comprises administering to the patient a composition comprising an effective anti-oxidation amount of an apolipoprotein (apo) A-IV to inhibit the progression of atherosclerosis. The apolipoprotein A-IV peptide is from 6 to 71 amino acids in length and has substantially the same lipid oxidation properties as the apolipoprotein A-IV molecule.

Independent claim 14 is directed to a method of treating a patient for atherosclerosis. The method comprises administering to the patient a composition comprising an effective anti-oxidation amount of an apolipoprotein (apo) A-IV peptide. The apolipoprotein A-IV peptide is from 6 to 71 amino acids in length. The peptide has substantially the same lipid oxidation properties as the apolipoprotein A-IV molecule.

First, Applicants submit that the Examiner has overlooked teachings in the present application as to structural features shared by the peptides employed in the present inventive methods. The Examiner has further failed to take notice of the disclosure of a representative number of species of the peptides, as well as disclosure related to at least one portion of the apo A-IV molecule important to the efficacy of the peptides. In particular, Applicants point to page 6, paragraph 2, wherein it is taught that "[t]he peptides of the present invention...comprise at least a six amino acid sequence derived from the amino terminal portion of the mature apolipoprotein A-IV."

In addition, it is explicitly disclosed that the larger inventive peptides of 15 and 90 amino acids "each contain within its sequence the aforementioned repeat sequence." Over a dozen representative peptides are disclosed in detail on pages 7-8. Further, page 22 provides specific guidance as to how a person of ordinary skill in the art may design a peptide as employed by the present inventive methods, that retains biological functioning and therefore efficacy (page 22, first full paragraph), with a reasonable expectation of success. Applicants set forth guiding principles that, when taken with knowledge common to those skilled in the art, as noted, permit the synthesis of the peptides according to the present inventive methods by one of ordinary skill in the art. Applicants also note that only routine, non-inventive

experimentation may be required to confirm the retention of the requisite biological functioning.

The specification at pages 23-25 sets forth descriptions of technologies known in the art which may be used by a person of ordinary skill in the art to synthesize the designed peptides. A preferred mode of synthesis is set forth at the bottom of page 24, the "Merrifield solid phase technique," along with a general description of the technique. Specific synthetic details are set forth in the last paragraph of page 25, bridging to page 26.

Applicants emphatically point out that the synthetic means related to production of the peptides according to the present invention are not aspects of the present inventive methods and are within the practice capability of persons of ordinary skill in the art. Indeed it is contemplated that other means will be developed that may be equivalent or superior with respect to peptide synthesis than those known today. The present specification provides ample guidance as to the design of the peptides, as well as over a dozen representative examples, and the synthesis is easily achieved by methods well-known in the art.

With respect in particular to claim 4, Applicants note that the scope of claim 4 is narrower than that of claim 1, and fail to understand the Examiner's assertion that the scope includes undefined variants and fragments having an unknown impact on the functioning and efficacy of the peptide. On the contrary, the method of claim 4 still includes the limitations of claim 1, which are practiced according to the specification guidelines. That is, the peptide still has the overall size limitations recited in claim 1, the peptide still must be designed to exhibit the requisite efficacy according to the guidelines set forth in the disclosure on pages 22, and 6-7. It is the Applicants position that methods employing peptides comprising this specified sequence and meeting the limitations of claim 1 are efficacious in inhibiting lipid

oxidation associated with a condition in a patient. Applicants disclose experiments with results that fully support this. Applicants inventive methods do not include employment of undefined and unsupported "variants and fragments" as asserted by the Examiner. Applicants respectfully submit that the Examiner failed to acknowledge or consider any of the disclosure cited above that relates to peptide design and/or retention of efficacy, and therefore came to the conclusion of insufficient written description erroneously.

According to case law governing the application of the written description requirement, a sufficient description of a genus may be achieved in several ways. One of them is by disclosure of a "representative number" of species. Another is "by recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Applicants respectfully point out that this requirement is notably not a conjunctive, but an either/or. *Regents of the University of California v. Eli Lilly & Company*, 119 F.3d 1559, 1569, 43 U.S.P.Q. 2d 1398, 1406 (Fed. Cir. 1997). This case law is cited approvingly in the USPTO's "Revised Interim Written Description Guidelines," Example 7. Regardless, Applicants have set forth both. Applicants list over a dozen representative species of peptides successfully employed in the methods according to the present invention. Further, Applicants provide ample guidance in the specification that may be referred to by a person of ordinary skill in the art in designing a peptide with efficacy according to the present inventive methods, with a reasonable expectation of success.

It is therefore submitted that present claims 1, 4-14, 19 and 64 are fully supported by the written description whereby the rejection under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

35 U.S.C. § 112, first paragraph "enablement"

Claims 1, 4-14, 19 and 64 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification, while being enabling for a method for inhibiting lipid oxidation associated with a condition in a patient comprising administering an apo A-IV compound, does not reasonably provide enablement for a method of inhibiting lipid oxidation comprising administering "all apo A-IV variants/fragments," such that the specification does not enable persons skilled in the art to make and/or use the invention commensurate in scope with the claims. Specifically, the Examiner lists 8 factors considered in an analysis determining whether undue experimentation is required to practice the invention. In particular, the Examiner asserts that "the specification needs to provide specific guidance on the treating conditions such as the dosage, the time and effect for treating conditions associated with lipid oxidation for various apo A-IV protein products, to be considered enabling for variants." This rejection is traversed and reconsideration is respectfully requested.

First, with respect to the Examiner's statement that while the present disclosure is "enabling for a method for inhibiting lipid oxidation associated with a condition in a patient comprising administering an apo A-IV compound," it does not enable methods involving administration of all apo A-IV "variants/fragments, Applicants respectfully submit that the Examiner's analysis of "undue experimentation" fails to acknowledge or consider disclosure in the present specification that is critically relevant to this analysis, and, indeed, it appears from the Examiner's comments that the very existence of this disclosure was entirely overlooked.

As noted and cited above, the present specification provides ample guidance on how to design the peptides derived from apo A-IV in order to retain efficacy with respect to

inhibition of lipid oxidation. The specification provides length, derivation portion, and amino acid selection guidance, as well as preferred methods of synthesis and experimental evidence in support of these design selective mechanisms. Indeed, Applicants disclose over a dozen such peptides, having lengths that vary substantially commensurate with the length limitation recited, deriving from the disclosed portion of the native apo A-IV molecule, and exhibiting the requisite efficacy. This disclosure hardly suggests that "all variants and fragments" of apo A-IV are equally desirable or even suitable for employment in the present inventive methods.

Hence, factors 1-4, as considered by the Examiner in the "undue experimentation" analysis, were factually misconstrued as most of the disclosure relevant to an analysis of these factors was not noted or considered. In addition, with respect to the analysis of factor 8, due to an omission of facts from the analysis, the Examiner further misconstrued the breadth of the instant claims. The claims simply do not recite every and all "fragment" or "variant" of apo A-IV.

The Examiner also suggests that the absence of "working examples" with respect to the treatment of conditions associated with inhibition of lipid oxidation, and the lack of specified dosage, regimen, time and treatment schedule, as well as failure to disclose "an expected outcome," are fatal to the enablement of method claims directed to treatment of conditions. Indeed, the Examiner explicitly states that "the specification needs to provide specific guidance on the treating conditions such as dosage, the time and effect for treating conditions associated with lipid oxidation for various apo A-IV protein products to be considered enabling for variants." Applicants respectfully submit that, aside from the fact that the Examiner has once again overlooked relevant disclosure, the Examiner also appears to have re-written USPTO practice on the enablement of methods of treating.

With respect to what Applicants disclose, dosage guidance is set forth on paged 26 and 31 of the present specification (page 26, first and second full paragraphs, page 31, last paragraph). Detailed administration guidelines and formulation guidelines are provided on pages 26-31. Admittedly, comporting with common PTO practice and due in part to the nature of the therapeutic arts, Applicants disclose this information with the caveat that such end uses must be determined according to specific concerns of the patient and practitioner. Under the pretext of this caveat, however, guidelines for the manufacture of pharmaceutical compositions and products are also provided, for example, on page 33.

With respect to "working examples," Applicants draw the Examiner's attention to the fact that what the Examiner appears to consider necessary to enable a treatment method is really the subject matter of disclosures submitted to regulatory agencies in the form of clinical data. Never, to the knowledge of the present Applicants, has the USPTO required that clinical data supporting efficacy, bioavailability, and/or specific treatment regimens such as timing, dosing, and administration route, be submitted in order to enable claims to a treatment method employing an active agent intended to be administered to a patient. Indeed, under the present drug regulatory scheme, it is unlikely that an applicant could lawfully generate such data prior to filing a patent application. Within the constraints of dealing with prophetics in this regard, Applicants have disclosed treatment regimens, dosages, suggested routes of administration, and other matters of clinical concern, taking into consideration the nature of the conditions disclosed as treatable by these actives, and the properties of the actives themselves. Applicants further submit that it is well within the ability of a person of ordinary skill in the medicinal and therapeutic arts to determine optimum dosages, suitable composition excipients and additives, suitable forms for administration, and the like, by routine experimentation and knowledge common to the art.

In the present "Background" section of the specification, Applicants carefully set forth a detailed explanation of the basis for an expectation that practice of the inventive methods will effectively inhibit lipid oxidation in conditions associated with lipid oxidation, inhibit the progression of atherosclerosis in a patient, and treat, inter alia, atherosclerosis in a patient. Applicants are therefore unsure of the basis for the Examiner's assertion that, with respect to treatment, no "expectation of outcome" has been disclosed.

The enablement requirement of §112, first paragraph, as judicially interpreted by case law, requires that the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *CFMT, Inc. v. Yieldup Int'l Corp.*, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003); *In re Wands*, 8 USPQ2d 1400, 1405 (Fed. Cir. 1988). "The key word is 'undue,' not experimentation.'" *Wands*, 8 USPQ2d at 1405 (citation omitted). That is, the specification need only teach those aspects of the invention that one skilled in the art could not discern without undue experimentation. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 49 USPQ2d 1671, 1673 (Fed. Cir. 1999) ("The scope of enablement ...is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation"); *Wands*, 8 USPQ2d at 1404-1405 ("Enablement is not precluded by the necessity for some experimentation such as routine screening.").

Applicants submit that it is within the ability of a person of ordinary skill in the protein arts to design an apo A-IV peptide according to the presently disclosed guidelines and illustrative examples, and determine whether that peptide is efficacious with respect to inhibiting lipid oxidation. The specification provides ample guidance, through the general disclosure, and through both specific and prophetic examples, as to how to practice the inventive methods which employ the defined peptides. A person of ordinary skill in the art

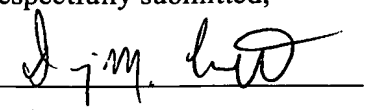
would have a reasonable expectation of success in designing a peptide employable in the present inventive methods by reference to the present specification, taken with knowledge common to the art.

Moreover, Federal Circuit precedent is clear. Enablement does not require that the specification describe how to make and use every possible variant of the claimed invention. Knowledge common to the art may fill in gaps and provide a means to interpolate between embodiments. Applicants agree that where extrapolation beyond disclosed embodiments is necessary to practice claimed embodiments, the predictability of the art may become a dispositive factor and defeat enablement, but, as here, where mere interpolation may be necessary, and the specification has disclosed numerous examples that extend, in design attribtues, across the breadth of the scope of the invention as defined by the claims, the predictability of the art is not a significant factor in predicting the successful development and employment of non-explicitly disclosed embodiments.

Hence, the rejection of claims 1, 4-14, 19 and 64, under 35 U.S.C. §112, first paragraph, for lack of enablement by the specification has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejection of the claims under 35 U.S.C. §§112, first paragraph, "written description" and "enablement" clauses, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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